PTO/SB/21 (09-06)
Approved for use through 03/31/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	51

Application Number	09/435,576
Filing Date	November 8, 1999
First Named Inventor	Chen et al.
Art Unit	1616
Examiner Name	Sharmila S. Gollamudi
Attorney Docket Number	141-594

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☑ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☑ Other Enclosure(s) (please Identify below):
  Return Receipt Postcard

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	HEDMAN & COSTIGAN, P.C.		
Signature			
Printed name	Martin P. Endres		
Date	July 24, 2007	Reg. No.	35,498

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below:

Signature			
Typed or printed name	Martin P. Endres	Date	July 24, 2007

A12
D

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	09/435,576
Applicant	:	Chih-Ming CHEN, et al.
Filed	:	November 8, 1999
TC/A.U.	:	1616
Examiner	:	Sharmila S. Gollamudi
Docket No.	:	300.1003
Customer No.	:	23280
For	:	**HMG-COA REDUCTASE INHIBITOR EXTENDED RELEASE FORMULATION**

Mail Stop: Appeal Brief
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

July 24, 2007

APPELLANTS AMENDED BRIEF ON APPEAL UNDER 37 C.F.R. §1.192

Sir:

Appellants submit this amended brief for the consideration of the Board of Patent Appeals and Interferences in support of their appeal of the Office Action dated November 30, 2006 in the above-identified application. A Notice of Appeal and a Response under 37 C.F.R. §1.116 were filed on November 21, 2005, with the statutory fee of $500.00, and received by the United States Patent and Trademark Office on November 23, 2005. A Supplemental Response was filed on April 7, 2006. A further supplemental response were filed on May 23, 2006 and accompanied by non-patent literature (A copy of the Physician's Desk Reference). An Appeal Brief with the statutory fee of $500.00 was also filed on May 23, 2006. The Appeal Brief was deemed non-compliant, as it made reference to the non-patent literature submitted in the May 23, 2006 Supplemental Response. The May 23, 2006 Supplemental Response was resubmitted on September 5, 2006, and considered on September 8, 2006.

A new Notice of Appeal was filed concurrently with Appellants Brief on Appeal on February 28, 2007. The Examiner's Answer to the February 28, 2007 Brief on Appeal issued on May 24, 2007. On June 28, 2007 a Notification of Non-Compliant Appeal Brief (37 C.F.R. 41.37) was mailed indicating that the February 28, 2007 Brief on Appeal failed to contain a concise explanation of the subject matter in independent claim 51. The present Amended Brief on Appeal only adds the requested concise explanation of the subject matter in independent claim 51[1]. Applicants apologize for any inconvenience this inadvertent omission may have caused.

It is believed that no fee is due with the submission of this Amended Brief on Appeal, as fees for the Notice of Appeal and for the filing of an Appeal Brief as set forth in 37 CFR 41.20 have been previously paid. If it is deemed that any fees are due in connection with the submission of this Appeal Brief, the Commissioner is hereby authorized to charge such deficiencies to Attorney Deposit Account No. 081540.

[1] This application was recently transferred from the firm of Davidson, Davidson & Kappell, LLC to Hedman & Costigan P.C. A substitute power of attorney will be submitted shortly.

TABLE OF CONTENTS

I. REAL PARTY IN INTEREST

The real party in interest is Andrx Labs LLC, a U.S. company having a place of business at 4955 Orange Drive, Davie, FL 33314, USA, assignee of the entire right, title, and interest in the above-identified patent application; and the licensee, Sciele Pharma, Inc., a U.S. company having a place of business at Five Concourse Parkway Suite 1800 Atlanta, GA 30328.

The invention was assigned by the inventors Chih-Ming Chen, Joseph Chou, and David Wong to Andrx Corporation. The assignment from the inventors to Andrx Corporation was recorded on November, 8, 1999 at reel 010385, frame 0949. The invention was then assigned from Andrx Corporation to Andrx Labs, LLC. The assignment from Andrx Corporation to Andrx Labs LLC was recorded on February 25, 2003 at reel 013788, frame 0187.

II. RELATED APPEALS AND INTERFERENCES

Appellants and their legal representatives and assignee are not aware of any appeal or interference that directly affects, will be directly affected by, or will have a bearing on the decision in this appeal.

III. STATUS OF CLAIMS

Claims 1-13, 18-19, 21-22, 25-29, 31-54, 57-71 and 76-81 are pending in this application. No claims have been allowed, all claims being subject to rejections in a Final Office Action dated July 21, 2005, Advisory Actions dated December 22, 2005 and April 26, 2006, and an Office Action dated November 30, 2006, and it is from this Final Office Action, subsequent Advisory Actions and most recent Office Action that this Appeal is taken. Claims 1-13, 18-19, 21-22, 25-29, 31-54 and 76-81 remain in the application and are appealed. A copy of these appealed claims is attached hereto as an Appendix.

IV. STATUS OF AMENDMENTS

In the Response under 37 C.F.R. §1.116 filed November 21, 2005, and the Supplemental Responses filed April 7, 2006 and May 23, 2006, the claims were not amended. In the Advisory Action dated December 22, 2005, the Examiner indicated that the claims remain rejected as set forth in the Final Office Action of July 21, 2005. In the Advisory Action dated April 26, 2006, the Examiner indicated that the rejection under 35 U.S.C. § 112, first paragraph was withdrawn in view of Applicants' arguments. In the November 30, 2006 Office Action, the Examiner indicated that the provisional obviousness-type double patenting rejection over copending Application No. 10/603,254 was withdrawn in view of the Terminal Disclaimer filed May 26, 2006.

V. SUMMARY OF CLAIMED SUBJECT MATTER

A. Claim 1

Independent claim 1 recites a controlled release oral solid dosage form for the reduction of serum cholesterol levels in humans comprising a drug comprising an alkyl ester of hydroxy substituted naphthalenes. See specification *e.g.* at page 3, lines 7-13.

Claim 1 further recites that the dosage form comprises a controlled release carrier in an amount effective to provide a controlled release of the drug. See specification *e.g.* at page 4, lines 13-14.

Claim 1 further recites the dosage form providing a mean time to maximum plasma concentration (T_{max}) of the drug which occurs at 10 to about 32 hours after oral administration to human patients. See specification *e.g.* at page 4, lines 15-16 and page 19, lines 39-42.

Claim 1 further recites the dosage form providing a reduction in serum cholesterol levels when administered to human patients on a once-a-day basis. See specification *e.g.* at page 4, lines 17-18 and Table 12 at page 52.

B. Claim 48

Independent claim 48 recites a method for reducing serum cholesterol levels in humans, comprising orally administering a drug comprising an alkyl ester of hydroxy substituted naphthalenes in a controlled release oral solid dosage form. See specification *e.g.* at page 3, lines 22-28.

The method of claim 48 further recites that the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the drug which occurs at 10 to about 32

hours after oral administration of the dosage form to human patients. See specification *e.g.* at page 4, lines 15-16 and page 19, lines 39-42.

C. Claim 51

Independent claim 51 recites a method for reducing serum cholesterol levels in humans, comprising orally administering a drug comprising an alkyl ester of hydroxy substituted naphthalenes in a controlled release oral solid dosage form in the morning. See specification *e.g.* at page 7, lines 22-28.

The method of claim 51 further recites that the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the drug which occurs at about 11 to about 32 hours after oral administration of the dosage form to human patients in the morning. See specification *e.g.* at page 7, lines 22-28, page 11, lines 23-27, and page 40, line 22 to 41, line 5.

D. Claim 58

Independent claim 58 recites a method for reducing serum cholesterol levels in humans, comprising orally administering a drug comprising an alkyl ester of hydroxy substituted naphthalenes in a controlled release oral solid dosage form to human patients at dinner time. See specification *e.g.* at page 8, lines 16-18.

Claim 58 further recites that the dosage form provides a mean time to maximum plasma concentration (T_{max}) at 10.4 to about 20.6 hours after oral administration of a single dose to a population of human patients. See specification *e.g.* at page 8, lines 19-20.

E. Claim 62

Independent claim 62 recites a method for reducing serum cholesterol levels in humans, comprising orally administering a drug comprising an alkyl ester of □ydroxyl substituted naphthalenes in a controlled release oral solid dosage form to human patients at bedtime. See specification *e.g.* at page 9, lines 1-3.

The method of claim 62 further recites that the dosage form provides a mean time to maximum plasma concentration (T_{max}) which occurs at 10 to about 23.2 hours after oral administration. See specification *e.g.* at page 9, lines 4-5.

F. Claim 70

Independent claim 70 recites a method for improving the dose-response relationship achieved via the administration of a statin drug orally administered in immediate release form. See specification *e.g.* at page 9, lines 22-23.

The method of claim 70 further recites by orally administering the statin in a controlled release dosage form which provides a mean time to maximum plasma concentration (T_{max}) of the statin drug which occurs at 10 to about 32 hours after oral administration to human patients. See specification *e.g.* at page 9, lines 24-26.

G. Claim 71

Independent claim 71 recites a method for providing increased systemic bioavailability of lovastatin, while at the same time not increasing the bioavailability of lovastatin acid, compared to an immediate release reference standard form of lovastatin. See specification *e.g.* at page 10, lines 22-25.

The method of claim 71 recites the step of preparing a controlled release oral solid dosage form of lovastatin which comprises a therapeutically effective amount of lovastatin and a sufficient amount of a controlled release carrier. See specification *e.g.* at page 10, lines 25-27.

The method of claim 71 further recites that the dosage form provides a dissolution of:

from about 0% to about 25% lovastatin released after 2 hours; see specification *e.g.* at page 10, lines 27-28;

from about 40% to about 85% lovastatin released after 6 hours; see specification *e.g.* at page 10, lines 28-29; and

not less than about 75% lovastatin released after 16 hours; see specification at page 10, line 29.

The dissolution rate recited in claim 71 is measured in vitro in a Type 2 USP 23 dissolution apparatus in 2% sodium lauryl sulfate, pH buffer to 7.0 at 37°C and 50rpm. See specification *e.g.* at page 11, lines 1-2.

The method of claim 71 further recites that the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the lovastatin from 10 to about 32 hours after oral administration to human patients, and administering the dosage form to human patients on a once-a-day basis. See specification *e.g.* at page 11, lines 2-5.

H. Claim 76

Independent claim 76 recites a controlled release oral solid dosage form for the reduction of serum cholesterol levels in humans comprising a therapeutically effective amount of lovastatin and a controlled release carrier. See specification *e.g.* at page 3, lines 7-13; page 4, lines 13-14; and page 6, lines 10-11.

The controlled release carrier of claim 76 is present in an amount effective to provide a controlled release of the lovastatin when the dosage form is orally administered. See specification *e.g.* at page 4, lines 13-14.

Claim 76 further recites that the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the lovastatin which occurs at 9.8 to about 18.8 (14.3 ±

4.5) hours after oral administration to human patients at bedtime. See specification *e.g.* at page 45, Table 6.

I. Claim 77

Independent claim 77 recites a controlled release oral solid dosage form for the reduction of serum cholesterol levels in humans comprising a therapeutically effective amount of lovastatin and a controlled release carrier. See specification *e.g.* at page 3, lines 7-13; page 4, lines 13-14; and page 6, lines 10-11.

The controlled release carrier of claim 77 is present in an amount effective to provide a controlled release of the lovastatin when the dosage form is orally administered. See specification *e.g.* at page 4, lines 13-14.

Claim 77 further recites that the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the lovastatin which occurs at 10.6 to about 23.2 (16.9 ± 6.3) hours after oral administration to human patients at bedtime. See specification *e.g.* at page 45, Table 6.

J. Claim 78

Independent claim 78 recites a method for reducing serum cholesterol levels in humans, comprising orally administering a therapeutically effective amount of lovastatin in a controlled release oral solid dosage form to human patients at bedtime. See specification *e.g.* at page 3, lines 7-13; page 4, lines 13-14; and page 6, lines 10-11.

The method of claim 78 further recites that the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the lovastatin which occurs at 9.8 to about 18.8 (14.3 ± 4.5) hours after oral administration to human patients at bedtime. See specification *e.g.* at page 45, Table 6.

K. Claim 79

Independent claim 79 recites a method for reducing serum cholesterol levels in humans, comprising orally administering a therapeutically effective amount of lovastatin in a controlled release oral solid dosage form to human patients at bedtime. See specification *e.g.* at page 3, lines 7-13; page 4, lines 13-14; and page 6, lines 10-11.

The method of claim 79 further recites that the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the lovastatin which occurs at 10.6 to about 23.2 (16.9 ± 6.3) hours after oral administration to human patients at bedtime. See specification *e.g.* at page 45, Table 6.

L. Claim 80

Independent claim 80 recites a controlled release oral solid dosage form for the reduction of serum cholesterol levels in humans comprising a therapeutically effective amount of lovastatin and a controlled release carrier. See specification *e.g.* at page 3, lines 7-13; page 4, lines 13-14; and page 6, lines 10-11.

The controlled release carrier of claim 80 is present in an amount effective to provide a controlled release of the lovastatin when the dosage form is orally administered. See specification *e.g.* at page 4, lines 13-14.

Claim 80 further recites that the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the lovastatin which occurs at 10.4 to about 20.6 (15.5 ± 5.1) hours after oral administration to human patients with the evening meal. See specification *e.g.* at page 45, Table 6.

M. Claim 81

Independent claim 81 recites a method for reducing serum cholesterol levels in humans, comprising orally administering a therapeutically effective amount of lovastatin

in a controlled release oral solid dosage form to human patients at bedtime. See specification *e.g.* at page 3, lines 7-13; page 4, lines 13-14; and page 6, lines 10-11.

The method of claim 81 further recites that the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the lovastatin which occurs at 10.4 to about 20.6 (15.5 ± 5.1) hours after oral administration to human patients with the evening meal. See specification *e.g.* at page 45, Table 6.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The following grounds of rejection are presented for appeal:

(1) Claims 1-13, 18, 19, 21, 22, 25-54, 57-71, and 76-81 have been rejected under 35 U.S.C. § 102(b) on the grounds of being anticipated by U.S. Patent No. 5,376,383 to Alberts et al.

(2) Claims 1-13, 18, 19, 21, 22, 25-29, 31-54, 57-71, and 76-81 have been rejected under 35 U.S.C. § 103(a) on the grounds of being obvious over U.S. Patent No. 5,837,379 to Chen et al. by itself or in view of Cheng et al. (Evaluation of Sustained/Controlled Release dosage forms of 3-Hydroxy-3-Methylglutaryl-Coenzyme A (HMG-CoA) Reductase Inhibitors in Dos and Humans, Pharmaceutical Research (1993), 10:1683-1687).

(3) Claims 1-13, 18, 19, 21, 22, 25-47, 76-77, and 80 have been rejected on the grounds of being unpatentable under the judicially created doctrine of obvious-type double patenting over claims 1-12 of U.S. Patent No. 6,485,748 to Chen et al. in view of Remington's Pharmaceutical Science (18th Edition, 1990).

VII. ARGUMENT

A. 35 U.S.C. §102 Rejection of Claims 1-13, 18-19, 21-22, 25-54, 57-71, and 76-81 Based Upon U.S. Patent No. 5,376,383 to Alberts et al.

1. The Examiner's rejection

The first issue presented is whether claims 1-13, 18, 19, 21, 22, 25-54, 57-51, and 76-81 are unpatentable under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,376,383 to Alberts et al. (hereinafter "the Alberts reference"). In the Final Office Action, the Examiner stated the following:

> Alberts discloses a method of lowering plasma cholesterol levels by administering to a subject a time-controlled drug-delivery device containing a water-soluble HMG-CoA reductase inhibitor (lovastatin, pravastatin, etc.). Alberts discloses that using a sustained or controlled release provides for a single dose to yield an equivalent or improved effect as that of a rapid release formulation (col. 1, lines 39-50 and abstract). . . . The examples provide a controlled device comprising a core and a coat, which is substantially similar to instant disclosure Table 1's general formula.
>
> Note that although the prior art does explicitly state the instant functional limitations, it is the examiner's position that the instant functional limitation is inherent since Albert's example 10 provides a release rate over an 18 hour period. Thus, the Tmax would inherently fall within [the] instant range. The recitation of a newly discovered function inherently possessed by the prior art, doe not make distinguish it from the prior art. Further it is applicant's burden to prove otherwise.

Final Office Action of July 21, 2005 at pages 3-4 (*citations omitted*).

In the December 22, 2005 Advisory Action, the Examiner responded to Appellants arguments in the November 21, 2005 Response to Final Office Action, as follows:

> With regard to the 102 rejection over Alberts, the examiner points out that, the examiner has made a reasonable rationale for inherency and it

> is the applicants burden to prove it is not inherent with evidence. Note MPEP 716.01 II wherein it clearly states that the attorney arguments cannot [take] the place of evidence.

Advisory Action of December 22, 2005 at page 2.

In the April 26, 2006 Advisory Action, the Examiner responded to Appellants' arguments presented in the April 7, 2006 Supplemental Response as follows:

> As indicated in the Final Office Action, Table 1 provides the structure, which provides the instant functional limitations. The device provided in Table 1 only requires a core and an outer coating. The seal coat, an inner coat, and overcoat are not required since the claimed range encompasses zero. Zero clearly implies that the coating is not required. Therefore, examiner points out that the instant structure as defined in Table 1 and that of the prior art are substantially the same used for the same purpose. With regard to the water-soluble polymer, Alberts examples utilize a water soluble polymer in the core. Therefore, the examiner has made a reasonable rationale for inherency. With regard to McClelland's structure is not similar to Albert's structure as argued by applicant.

Advisory Action of April 26, 2006 at page 2.

In the November 30, 2006 Office Action, the Examiner further responded to Appellants' arguments presented in the April 7, 2006 Supplemental Response as follows:

> The Examiner acknowledges that McClelland's device is similar to the device disclosed in Example 3 of US '383. However, the examiner points out that example 3 has a release of less than 14 hours and the examiner's rationale is based on example 10, which has a release over an 18-hour period and the same core as disclosed in the instant specification.
>
> Applicant argues that Lescol is a once a day controlled release dosage form of fluvastatin and has a Tmax of 2.5 to 3 hours and thus not all controlled release dosage form comprising hydroxyl naphthalene will inherently have the instant Tmax.

> The relevance of this argument is unclear since Lescol s not the product taught in US [383]; thus this is not a comparison of the closest prior art.

November 30, 2006 Office Action at pages 4-5.

2. U.S. Patent No. 5,376,383 to Alberts et al. does not anticipate the claims

a. Claims 1-13, 18-19, 21-22, 25-54, 57-71, and 76-81

Appellants respectfully submit that the Alberts reference does not inherently teach the claimed T_{max} parameters as recited in the present claims.

Specifically, the Alberts reference does not inherently teach a controlled release dosage form of the present invention or a method of treatment with a controlled release dosage form of the present invention, which provides the following:

a. a mean time to maximum plasma concentration (T_{max}) of the drug which occurs at 10 to about 32 hours after oral administration as recited in claims 1, 48, 70, and 71;

b. a mean time to maximum plasma concentration (T_{max}) which occurs at about 11 to about 32 hours after oral administration as recited in claim 51;

c. a mean time to maximum plasma concentration (T_{max}) at 10.4 to about 20.6 hours after oral administration as recited in claim 58;

d. a mean time to maximum plasma concentration (T_{max}) which occurs at 10 to about 23.2 hours as recited in claim 62;

e. a mean time to maximum plasma concentration (T_{max}) of lovastatin which occurs at 9.8 to about 18.8 (14.3 ± 4.5) hours after oral administration to human patients at bedtime as recited in claims 76 and 78;

f. a mean time to maximum plasma concentration (Tmax) of lovastatin which occurs at 10.6 to 23.2 (16.9 ± 4.5) hours after oral administration to human patients at bedtime as recited in claims 77 and 79; or

g. a mean time to maximum plasma concentration (Tmax) of lovastatin which occurs at 10.4 to about 20.6 (15.5 ± 5.1) hours after oral administration to human patients with the evening meal as recited in claims 80 and 81.

In support of this position, submitted herewith is Gregory A. McClelland, et al., Enhancement of 3-Hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) Reductase Inhibitor Efficacy Through Administration of a Controlled-Porosity Osmotic Pump Dosage Form, Pharmaceutical Research, Vol. 8., No. 7. 1991, which was submitted in the Appellants response dated April 7, 2006. As admitted by the Examiner in the November 30, 2006 Office Action, the McClelland structure is similar to Albert's structure,

McClelland et al. demonstrate *in vivo* data with respect to this formulation in Figure 2 on page 875, which depicts the peak of the plasma/concentration time curve at a time less than 5 hours. One skilled in the art would immediately recognize that this is not indicative of the T_{max} recited in the presently claimed invention (e.g., 10 to about 32 hours), to the extent that dog data is instructive with respect to humans.

Therefore, assuming arguendo that the Examiner has provided a reasonable rational to establish inherency, Appellants respectfully submit that they have met their burden to prove that the pharmacokinetic parameters are not inherent with evidence, as requested by the Examiner. The evidence provided by Appellants shows that Example 3 of Alberts is virtually identical to the formulation of McClelland et al. and that the in-vivo data in McClelland at al. is not indicative of the T_{max} of the present invention (e.g., 10 to about 32 hrs). Therefore, by syllogism, Example 3 of Alberts would not inherently be indicative of the recited T_{max} (e.g., 10 to about 32 hrs), as it is virtually identical to the McClelland formulation.

Appellants submit that they have established that the claimed pharmacokinetic parameters are not inherent in the Alberts reference. In any event, Appellants respectfully submit that the Examiner did not establish a reasonable rational that the claimed pharmacokinetic parameters were inherent in the Alberts reference to begin with. To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it

would be so recognized by persons of ordinary skill." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 U.S.P.Q.2D (BNA) 1746, 1749 (Fed. Cir. 1991). "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* at 1269, 20 U.S.P.Q.2D (BNA) at 1749 (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981). See also, *In re Rijckaert* 9 F.3d 1531, 28 U.S.P.Q.2d (BNA) 1955 (Fed. Cir. 1993) (reversed rejection, finding inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art).

Appellants respectfully submit that the Examiner did not meet her burden of proof to make an inherency rejection, as there is no indication in the Alberts reference that the claimed T_{max} of the present invention must be "necessarily present" in the formulations described in the reference. It is further submitted that if one of ordinary skill in the art were able to manipulate the formulations of Alberts to achieve a formulation which met the present claimed limitations, one would have to optimize conditions, ingredients and parameters. For example, critical parameters such as compression force, particle size of initial ingredients, and temperature/humidity conditions are not specified in the Alberts reference.

To support her position that the Alberts reference inherently describes the presently claimed Tmax, the Examiner cited Example 10 of the Alberts reference in the July 21, 2005 Final Office Action and in the November 30, 2006 Office Action. However, Example 10 merely states that the formulation gave an 85% release over 18 hours, and fails to provide any indication or suggestion for correlating a mean time to maximum plasma concentration (T_{max}). "[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that must necessarily include the unstated limitation." *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006). Appellants submit that an 85% release over 18 hours does not indicate that the formulation therein "must necessarily including the unstated limitation", *i.e.* the claimed mean time to maximum plasma concentration (Tmax). For example, a formulation which provides an initial burst of active agent within the first few hours, could have an early Tmax (e.g., 1 or 2 hours) while still releasing 85% active agent at 18 hours.

In the November 30, 2006 Office Action, the Examiner questioned the relevance of Appellant's submission of the Lescol XL product information, as Lescol XL contains fluvastatin; an alkyl ester of a hydroxyl substituted naphthalene not specifically exemplified in the Alberts reference. However, the Examiner also appears to conclude that formulating any alkyl ester of a hydroxyl substituted naphthalene into a controlled release dosage form will necessarily provide the claimed T_{max} ranges (e.g., 10 to about 32 hours). Therefore, Appellants submit that the submission of the Lescol XL prescribing information is relevant, as claim 1 is not limited to lovastatin, but is directed to an alkyl ester of hydroxyl substituted naphthalene. The Prescribing Information for Lescol XL, submitted in the Appellants response dated May 23, 2006, shows that all alkyl esters of a hydroxyl substituted naphthalene will not inherently provide the claimed T_{max} ranges, as alleged by the Examiner.

Appellants respectfully point out that Lescol XL is a once-a-day controlled release dosage form of fluvastatin, an alkyl ester of a hydroxyl substituted naphthalene. As indicated in the Prescribing Information, Lescol XL provides peak concentration of fluvastatin within 2.5 to 3 hours post dose (i.e., a Tmax of 2.5 to 3 hours). This is in contrast to the T_{max} ranges (e.g., 10 to about 32 hours) provided by the present invention. In view of this information, Appellants respectfully submit that including a hydroxyl substituted naphthalene into a controlled release dosage form will not inherently provide the claimed T_{max} ranges (e.g., 10 to about 32 hours).

Further, the Examiner's "reasonable rationale" for establishing inherency is based on the misconception that the Alberts examples and the general formula of Table I of the present application are substantially the same. However, the formulations described by Alberts are remarkably different from those taught by the present application and therefore the conclusion that the Alberts formulations inherently disclose the pharmacokinetic parameters and dissolution profiles of the claimed controlled release dosage forms is incorrect.

Table I of the present application shows that a tablet that can be modified to exhibit the claimed pharmacokinetic parameters can contain a) an inner core containing an alkyl ester of a substituted naphthalene, a water swellable polymer, and an osmotic agent and b) an outer coating containing an enteric polymer and a water-insoluble

polymer. In contrast, Alberts describes tablets with cores that **do not** contain water swellable polymers (examples 3-7) and tablets that contain drug mixed with a water swellable polymer, but **do not** have an outer coating containing an enteric polymer and a water-insoluble polymer (examples 8-16).

The Examiner alleges that the coating is not required because Table I includes ranges which encompass zero. However, Appellants submit that the claims are not meant to encompass any formulation that may fall within the general ranges of Table I of the present application. Rather, the claims are meant to encompass only those formulations which exhibit the claimed T_{max} parameters. The exemplified formulations which exhibit the pharmacokinetic data of the instant claims contain a core, a seal coat, an inner coating containing an enteric polymer, an outer coating containing an enteric polymer and a water insoluble polymer, and an optional overcoat (see examples 5-9 on pages 35-38; pages 40-44; and tables 6-8). It is noted that the present claims are not limited to these exemplified formulations and that other formulations which exhibit the claimed pharmacokinetic parameters are encompassed by the claimed invention. For example, pages 19 to 24 of the present specification disclose many different types of formulations which can be modified to provide the claimed pharmacokinetic parameters.

In accordance with the above, Appellants respectfully submit that the Alberts reference does not teach or suggest the presently claimed compositions and methods which recite the claims T_{max} limitations.

In addition, Appellants respectfully submit that the Alberts reference does not teach or suggest the claimed method for improving the dose-response relationship achieved via the administration of a statin drug orally administered in immediate release form as recited in claim 70.

Applicants further submit that the Albert reference does not teach or suggest the claimed method for providing increased systemic bioavailability of lovastatin, while at the same time not increasing the bioavailability of lovastatin acid, compared to an immediate release reference standard form of lovastatin as recited in claim 71. The Alberts reference also does not teach or suggest the claimed dissolution parameters as recited in claim 71.

Accordingly, Appellants respectfully request that the rejection over the Alberts reference be removed.

B. 35 U.S.C. §103 Rejection of Claims 1-13, 18-19, 21-22, 25-29, 31-54, 57-71 and 76-81 Based Upon U.S. Patent No. 5,837,379 to Chen et al.

1. The Examiner's rejection

The second issue presented is whether claims 1-13, 18, 19, 21, 22, 25-29, 31-54, 57-71 and 76-81 are unpatentable under 35 U.S.C. §103(a) as being obvious over U.S. Patent No. 5,837,379 to Chen et al.

In the final Office Action, the Examiner stated the following:

> Chen et al disclose a once daily pharmaceutical tablet having a 1) compressed core contains a medicament, a water-soluble osmotic compound, and one or more osmotic polymers, and 2) a membrane coating containing a water insoluble pharmaceutically acceptable polymer and an enteric polymer. See abstract. Although nifedipine is exemplified, Chen teaches various water-insoluble medicaments that may be utilized, including instant lovastatin. See column 2, line 64.
>
> . . . .
>
> It is deemed obvious to one of ordinary skill in the art at the time the invention was made to look to the guidance provided by Chen et al and include the instant lovastatin in the controlled release dosage form. One would have been motivated to do so since Chen teaches a variety of medicaments that would benefit from the use of the instant controlled release formulation and teaches the instant active as one of the suitable medicaments. Therefore, one could reasonably expect similar results by including lovastatin in Chen's controlled release device.
>
> Furthermore, it is the examiner's position that the instant controlled release device would meet the instant functional limitations since Chen's controlled release device is similar in structure and formulation to applicant's dosage form described in the specification; in particular Table 1. Therefore, it is the examiner's position that both would function similarly if not the same since the structures of the instant invention and that of the prior art are the same.

Final Office Action of July 21, 2005 at pages 7-8.

In the December 22, 2005 Advisory Action, the Examiner responded to Appellants arguments in the response to Final Office Action as follows:

> With regard to the obviousness rejection over Chen, the examiner has not argued that nifedipine and lovastatin have similar structures, rather the examiner has argued that the controlled release dosage form taught by Chen is structurally similar to applicant's. Thus it is the examiner's position that the controlled release dosage form would provide the instantly claimed Tmax. The examiner notes that lovastatin is not exemplified and is taught as a suitable drug among other drugs, thus the examiner has made the rejection under obviousness wherein the criteria for obviousness is that the prior art provides some suggestion or motivation to utilize the instantly claimed drug. In instant case, Chen teaches lovastatin is a suitable drug to utilize in the dosage form.

Advisory Action of Dec. 22, 2005 at page 2.

In the April 26, 2006 Advisory Action, the Examiner responded to Appellants arguments in the April 7, 2006 Supplemental Response as follows:

> Although the pharmacokinetics of nifedipine are exemplified, a skilled artisan [] would have been motivated to substitute nifedipine with the instant lovastatin and expect similar pharmacokinetic values since Chen clearly suggests the use of other drugs in place of nifedipine.

April 26, 2006 Advisory Action at pages 2-3.

In the November 30, 2006 Office Action, the Examiner responded to Appellants' arguments in the April 7, 2006 Supplemental Response as follows:

> [T]he motivation of utilizing lovastatin is within the disclosure of Chen itself. The examiner points out that the selection of a drug is prima facie obviousness depending on the disease to be treated.
>
> . . .
>
> The examiner's position is that Chen's controlled release device is similar, if not same, to the instantly claimed controlled device and thus the prior

> art's controlled release device will meet the instantly claimed functional limitations including the instant Tmax. The premise is not that one would expect similar results since nifedipine and the instant alkyl esters of hydroxyl substituted napthalenes are the same.
>
> . . .
>
> Applicant argues that Lescol is a once a day controlled release dosage form of fluvastatin and has a Tmax of 2.5 to 3 hours and thus not all controlled release dosage form comprising hydroxyl naphthalene will inherently have the instant Tmax.
>
> The relevance of this argument is unclear since Lescol s not the product taught in US 379; thus this is not a comparison of the closest prior art.

November 30, 2006 Office Action at pages 10-13.

2. U.S. Patent No. 5,837,379 to Chen et al. does not render the claims obvious

a. Claims 1-13, 18-19, 21-22, 25-29, 31-54, 57-71 and 76-81

Appellants respectfully submit that Chen et al. fail to teach or suggest the present formulation comprising an alkyl ester of hydroxy substituted naphthalenes with the claimed pharmacokinetic parameters.

In rejecting the claims over Chen et al., the Examiner has again questioned the relevance of Appellant's submission of the Lescol XL product information, as Lescol XL contains fluvastatin; an alkyl ester of a hydroxyl substituted naphthalene not specifically exemplified in the Chen reference. However, the Examiner again appears to conclude that formulating any an alkyl ester of a hydroxyl substituted naphthalene into a controlled release dosage form will necessarily provide the claimed T_{max} ranges (e.g., 10 to about 32 hours). However, the Examiner also appears to conclude that formulating any alkyl ester of a hydroxyl substituted naphthalene into a controlled release dosage form will necessarily provide the claimed T_{max} ranges (e.g., 10 to about 32 hours). Therefore, Appellants submit that the submission of the Lescol XL prescribing information is relevant, as claim 1 is not limited to lovastatin, but is directed to an alkyl ester of hydroxyl substituted naphthalene. The Prescribing Information for Lescol XL, submitted in the Appellants response dated May 23, 2006, shows that all alkyl esters of a hydroxyl

substituted naphthalene will not inherently provide the claimed T_{max} ranges, as alleged by the Examiner.

As indicated in the Prescribing Information, Lescol XL provides peak concentration of fluvastatin within 2.5 to 3 hours post dose (i.e., a Tmax of 2.5 to 3 hours). This is in contrast to the T_{max} ranges (e.g., 10 to about 32 hours) provided by the present invention. In view of this information, Appellants respectfully submit that including a hydroxyl substituted naphthalene into a controlled release dosage form will not inherently provide the claimed T_{max} ranges (e.g., 10 to about 32 hours).

Appellants respectfully submit that Chen et al. fail in the very least to teach, hint or suggest the T_{max} range recited in the present claims. The only data provided in this patent directed to in-vivo results is data directed to dosage forms of nifidepine, which is not in any way related to, e.g., HMG-CoA Reductase Inhibitors. None of the exemplified formulations include a drug that is a HMG-CoA Reductase Inhibitor, and no information is provided in this reference concerning a desired time to maximum plasma concentration for any drug, let alone a HMG-CoA Reductase Inhibitor. Further, there is no statement in Chen et al. relating to T_{max}, and there is no suggestion in Chen et al. that the in-vivo plasma levels achieved in the examples of the reference would be desirable for controlled or sustained release formulations containing the class drugs known as alkyl esters of hydroxyl substituted napthalenes.

Appellants respectfully submit that it is only with the benefit of the disclosure of the present application, that one skilled in the art would be motivated to prepare a formulation that provides a time to maximum plasma concentration (T_{max}) as recited in the present claims. Accordingly, the Examiner used impermissible hindsight reasoning in making this rejection.

The physical characteristics (e.g., solubility, melting point) for any given drug are typically different. These characteristics must be considered in formulating the drug. Chen et al. does not exemplify any formulations containing an alkyl ester of hydroxy substituted naphthalene, nor does it provide any specific guidance with respect to formulating such an agent. For example, there is no teaching of compression forces or temperature and humidity processing parameters for preparing a formulation containing an alkyl ester of hydroxy substituted naphthalene. Therefore, assuming one skilled in the

art could formulate an alkyl ester of hydroxy substituted naphthalene in accordance with the teachings of Chen et al. to achieve the claimed T_{max} parameters, such formulation would be a result of optimization of conditions. Therefore the Examiner is incorrect to state that "... both would function similarly if not the same since the structures of the instant invention and that of the prior art are the same." See *In re Rijckaert* 9 F.3d 1531, 28 U.S.P.Q.2d (BNA) 1955 (Fed. Cir. 1993) (reversed rejection, finding inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art).

Further, Applicants note that the foundational facts for a prima facie case of obviousness are: (1) the scope and content of the prior art; (2) the difference between the prior art and the claimed invention; and (3) the level of ordinary skill in the art. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Moreover, objective indicia such as commercial success and long felt need are relevant to the determination of obviousness. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538, 218 U.S.P.Q. (BNA) 231, 236 (Fed. Cir. 1983).

Chen et al. is directed to controlled release dosage forms and only incidentally mentions lovastatin, fluvastatin, simvastatin, and pravastatin in an exhaustive list (see column 2, line 51 to column 3, line 11 of Chen et al.) of over <u>one hundred</u> possible agents including various classes of drugs and specific drugs in multiple forms (*e.g.*, salts, esters, etc.) and there is no motivation in Chen to produce dosage forms of these compounds having the claimed pharmacokinetic parameters. In contrast, the present application clearly demonstrates the benefits and need for these dosage forms in Table 12, which shows the advantage of a formulation of the present invention (Lovastatin XL) over immediate release Mevacor®, with respect to changes in LDL- cholesterol, HDL-cholesterol, Total Cholesterol, and Triglycerides.

Appellants respectfully submit that one skilled in the art would not be motivated to select the particular claimed agent (i.e., an alkyl ester of hydroxy substituted naphthalenes) from the large genus disclosed at column 2, line 51 to column 3, line 11 of Chen et al. In support of this position, it is respectfully submitted that with respect to Chen et al., (i) the size of the genus is <u>not sufficiently small</u> as to render each member of the genus inherently disclosed, (ii) the reference does <u>not expressly teach</u> a particular

reason to select the claimed agent; and (iii) there is no teaching of structural similarity in the reference. See MPEP 8th Edition, 2nd revision 2144.08 II (A)(4)(A-C). A discussion of these points follows:

(i) The size of the genus is not sufficiently small as to render each member of the genus inherently disclosed

The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). Some motivation to select the claimed species or subgenus must be taught by the prior art. See *e.g.*, *In re Deuel*, 51 F.3d 1552, 1558-59, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995).

It is respectfully submitted that the size of the possible active agents which can be used in accordance with Chen et al. is sufficiently large as not to inherently disclose each and every individual species (in this case, lovastatin, fluvastatin, simvastatin, and pravastatin) which falls within their broad genus.

(ii) The reference does not expressly teach a particular reason to select the claimed agent

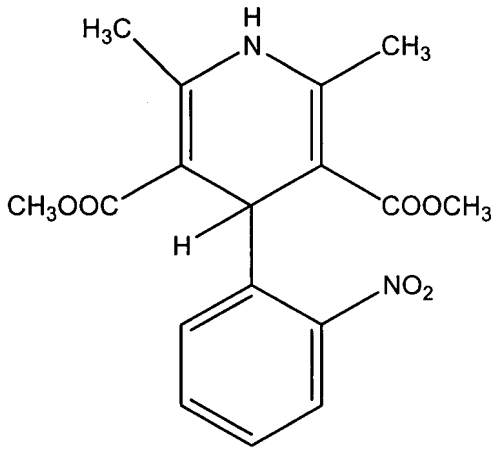
If a prior art reference expressly teaches a particular reason to select the claimed species, the Examiner should point out the express disclosure which would have motivated one of ordinary skill in the art to select the claimed species. See MPEP 8th Edition, 2nd revision 2144.08 II (A)(4)(B). It is respectfully submitted that the only recitation of lovastatin, fluvastatin, simvastatin, and pravastatin in Chen et al. is embedded within a large genus. Accordingly, the Chen et al. reference does not expressly teach a particular reason to select an alkyl ester of hydroxy substituted naphthalenes, such as lovastatin, from the plethora of other possible species in the genus of the reference.

(iii) There is no teaching of structural similarity in the reference

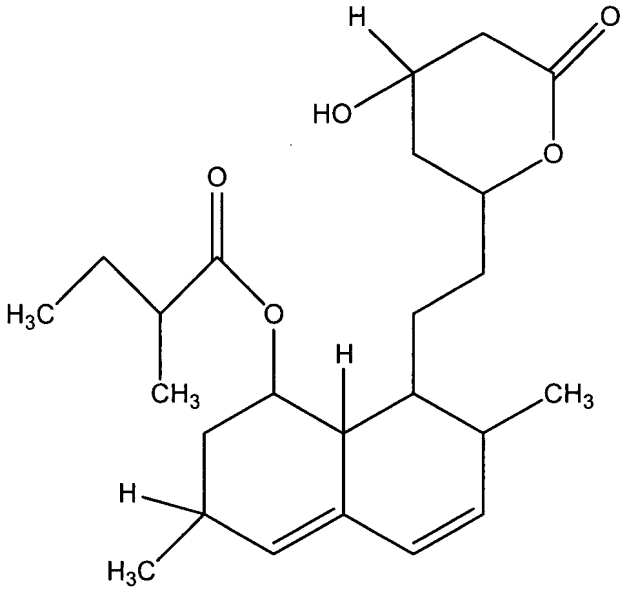
If a preferred species is structurally similar to that claimed, its disclosure may motivate one of ordinary skill in the art to choose the claimed species from the genus. See, *e.g.*, *In re Dillon*, 919 F.2d 688, 693, 696, 16 USPQ2d 1897, 1901, 1904 (Fed. Cir.

1990). It is noted that the preferred active agents exemplified in Chen et al. is nifedipine in Examples 1 and 2.

It is respectively submitted that nifedipine is not similar in structure to lovastatin, fluvastatin, simvastatin, and pravastatin (the alkyl esters of hydroxy substituted naphthalenes described in Chen) and does not provide similar pharmacological activity. Nifedipine is a calcium channel blocker which is used primarily for the treatment of hypertension, while lovastatin, fluvastatin, simvastatin, and pravastatin are HMG COA reductase inhibitors for the treatment of hypercholesterolemia. Structurally, nifedipine is a dihydropyridine compound and lovastatin, fluvastatin, simvastatin, and pravastatin are lactone based structures. In order to exemplify, the structures of these lovastatin and nifedipine are set forth below in order to show the dissimilar structures of these agents:



Nifedipine



Lovastatin

Accordingly, as Chen et al. does not teach any preferred species which have structural similarity to lovastatin, fluvastatin, simvastatin, and pravastatin, there is no motivation therein to one skilled in the art to select these agents from the large genus disclosed therein.

Although the Examiner stated that she has not argued that nifedipine and lovastatin have similar structures, but that the controlled release dosage form taught by

Chen et al is structurally similar to Appellants, the structure of the controlled release dosage form would ultimately be altered with the inclusion of lovastatin. The differences in structure, pharmacological properties, and characteristics, of the species of active agent would be considered by one or ordinary skill in the art in the preparation of a controlled release formulation. Any teaching or suggestion in the reference of a preferred species that is significantly different in structure from the claimed species weigh against selecting the later selected species. See, *e.g.*, *In re Baird*, 16 F.3d 382-83, 29 USPQ2d 1552 (Fed. Cir. 1994). Accordingly, the examples of Chen et al. directed to a compound (i.e. nifedipine) that is not structurally similar to lovastatin, fluvastatin, simvastatin, and pravastatin (as discussed above) is further evidence that one skilled in the art would not be motivated to select these compounds from the genus described therein.

The broad ranges described in the present specification at Table 1 provide guidance to one of ordinary skill in the art to prepare a dosage form of the present invention with routine experimentation. One skilled in the art would appreciate that formulations of alkyl esters of hydroxy substituted naphthalenes could be prepared that do not meet the limitations of claim 1, but would generically fall with the ranges of Table 1 of the present application.

In accordance with the above, Appellants respectfully submit that Chen at al. does not teach or suggest the presently claimed compositions and methods which recite the claimed T_{max} limitations.

In addition, Appellants respectfully submit that Chen et al. does not teach or suggest the claimed method for improving the dose-response relationship achieved via the administration of a statin drug orally administered in immediate release form as recited in claim 70.

Applicants further submit that Chen et al. does not teach or suggest the claimed method for providing increased systemic bioavailability of lovastatin, while at the same time not increasing the bioavailability of lovastatin acid, compared to an immediate release reference standard form of lovastatin as recited in claim 71. Chen et al. also does not teach or suggest the claimed dissolution parameters as recited in claim 71.

Therefore, as Chen et al. fails to teach or suggest the presently claimed invention, Appellants respectfully submit that the claims are patentable over Chen et al. and respectfully request that this rejection be reversed.

C. Obviousness-Type Double Patent Rejections based upon U.S. Patent No. 6,485,748.

1. The Examiner's rejection

The third issue presented is whether claims 1-13, 18, 19, 21, 22, 25-47, 76-77, and 80 are unpatentable over claims 1-12 of U.S. Patent No. 6,485,748 under the judicially created doctrine of obviousness-type double patenting. In the Final Office Action, the Examiner stated that "[a]lthough US patent '748 recites a generic slightly water-soluble drug, the specification defines lovastatin as a drug that falls within this category.

In the December 22, 2005 Advisory Action, the Examiner stated that ". . . the examiner notes that US patent does not claim the instant Tmax, however, the examiner notes that US patent's claimed dosage form is capable of providing the instantly claimed Tmax, " and further stated in the November 30, 2006 Office Action that the dosage forms of the instant application and that of the '748 patent "would function in a similar manner [] since both claim the same drug and the same controlled release structure."

2. The double patenting rejection over U.S. Patent No. 6,485,748 should be reversed.

a. Claims 1-13, 18, 19, 21, 22, 25-47, 76-77

Appellants note that when considering when the invention defined in the claim of an application is an obvious variation of the invention defined in the claims of a patent, the disclosure of the patent may not be used as prior art. However, the specification can be used as a dictionary to learn the meaning of a term in the patent claim, or be examined with respect to those portions which provide support for the claims (See MPEP 8th Edition, Revision 2, Section 804(2)(B)(1)).

It is respectfully submitted that the claims of the '748 patent fail in the very least to teach, hint or suggest the T_{max} ranges recited in the present claims. In addition, there

are no dependent claims directed to alkyl esters of hydroxy substituted naphthalenes or even the general class of HMG CoA reductase inhibitors. In fact, the only dependent claims directed to specific drugs are directed to calcium channel blockers (claims 2 and 3). Furthermore, the specification of the '748 patent, like that of the Chen et al. '379 patent, only incidentally mentions lovastatin, fluvastatin, simvastatin, and pravastatin in an exhaustive list (see column 2, line 58 to column 3, line 16 of the '748 patent) of over one hundred possible agents including various classes of drugs and specific drugs in multiple forms (*e.g.*, salts, esters, etc.). The only in-vivo data provided in the '748 patent is data directed to dosage forms of nifidepine, which is not in any way related to, *e.g.*, an alkyl ester of hydroxy substituted naphthalenes, as described above. None of the exemplified formulations include a drug that is an alkyl ester of hydroxy substituted naphthalenes, and no information is provided in this reference concerning a desired time to maximum plasma concentration for any drug, let alone an alkyl ester of hydroxy substituted naphthalenes. Moreover, there is no statement in either the specification or the claims of the '748 patent relating to T_{max}, or suggestion that the in-vivo plasma levels achieved in the examples of the reference would be desirable for controlled or sustained release formulations containing the class drugs known as alkyl esters of hydroxy substituted napthalenes.

Appellants respectfully submit that it is only with the benefit of the disclosure of the present application, that one skilled in the art would be motivated to prepare a formulation that provides a time to maximum plasma concentration (T_{max}) as recited in the present claims. Accordingly, the Examiner used impermissible hindsight reasoning in making this rejection.

Therefore, it is respectfully submitted that the claims of the '748 patent do not teach or suggest the presently claimed invention Appellants respectfully request that the obviousness rejection over the '748 patent be reversed.

Conclusion

Applicants respectfully submit that for the foregoing reasons the final rejections of claims should be reversed, and that the present claims are in condition for allowances

Prompt consideration of the arguments presented herein and reversal of the final rejections is earnestly solicited.

Respectfully submitted,

Martin P. Endres
Reg. No. 35,498

MAILING ADDRESS:
HEDMAN & COSTIGAN, P.C.
1185 Avenue of the Americas
New York, NY 10036-2601
(212) 302-8989

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail on **July 24, 2007** in an envelope addressed to:

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Martin P. Endres Reg. No. 35,498

III. CLAIMS APPENDIX

Claim 1. (Previously presented) A controlled release oral solid dosage form for the reduction of serum cholesterol levels in humans comprising a drug comprising an alkyl ester of hydroxy substituted naphthalenes and a controlled release carrier in an amount effective to provide a controlled release of the drug, the dosage form providing a mean time to maximum plasma concentration (T_{max}) of the drug which occurs at 10 to about 32 hours after oral administration to human patients, the dosage form providing a reduction in serum cholesterol levels when administered to human patients on a once-a-day basis.

Claim 2. (Previously presented) The controlled release oral solid dosage form of claim 1, which includes an amount of a controlled-release carrier for said drug effective to release said drug in about 4 to 30 hours in vitro in a Type 2 USP 23 dissolution apparatus in 2% sodium lauryl sulfate, pH buffer to 7.0 at 37° C and 50rpm.

Claim 3. (Original) The controlled release oral solid dosage form of claim 1, which provides a dissolution of from about 0% to about 25% drug released after 2 hours; from about 40% to about 85% drug released after 6 hours; and not less than about 75% drug released after 16 hours, when measured in vitro in a Type 2 USP 23 dissolution apparatus in 2% sodium lauryl sulfate, pH buffer to 7.0 at 37° C and 50rpm.

Claim 4. (Original) The controlled release oral solid dosage form of claim 1, which provides a dissolution of from about 0% to about 20% drug released after 2 hours; from about 50% to about 80% drug released after 6 hours; and not less than about 80% drug

released after 16 hours, when measured in vitro in a Type 2 USP 23 dissolution apparatus in 2% sodium lauryl sulfate, pH buffer to 7.0 at 37°C and 50rpm.

Claim 5. (Original) The controlled release oral solid dosage form of claim 1, which provides a dissolution of from about 10% to about 15% drug released after 2 hours; from about 65% to about 75% drug released after 6 hours; and not less than about 79% drug released after 16 hours, when measured in vitro in a Type 2 USP 23 dissolution apparatus in 2% sodium lauryl sulfate, pH buffer to 7.0 at 37°C and 50rpm.

Claim 6. (Original) The controlled release oral solid dosage form of claim 1, which provides a mean time to maximum plasma concentration about 14 to about 24 hours after oral administration.

Claim 7. (Original) The controlled release dosage form of claim 1, wherein the drug is lovastatin, said dosage form providing a mean maximum plasma concentration (C_{max}) of lovastatin from about 1 ng/ml to about 8 ng/ml, based on a 40 mg dose of lovastatin, after administration to human patients.

Claim 8. (Original) The controlled release dosage form of claim 1, wherein the drug is lovastatin, said dosage form providing a maximum plasma concentration (C_{max}) of the drug of from about 3 ng/ml to about 4 ng/ml (based on a 40 mg dose of lovastatin), after administration to human patients.

Claim 9. (Previously presented) The controlled release dosage form of claim 1, wherein the drug is selected from the group consisting of lovastatin, mevastatin, pravastatin, simvastatin, and mixtures thereof.

Claim 10. (Original) The controlled release dosage form of claim 1, wherein the drug is lovastatin.

Claim 11. (Original) The controlled release dosage form of claim 1, wherein the drug is lovastatin in an amount of from about 10 to about 80 mg.

Claim 12. (Original) The controlled release dosage form of claim 1, wherein the drug is lovastatin, and the dosage form provides a mean $AUC_{0\text{-}48hr}$ of lovastatin from about 15 to about 90 ng·hr/ml.

Claim 13. (Original)The controlled release dosage form of claim 1, wherein the drug is lovastatin, and the dosage form provides a mean $AUC_{0\text{-}48hr}$ of lovastatin from about 34 to about 77 ng·hr/ml.

Claims 14-17. (Cancelled)

Claim 18. (Original) The controlled release dosage form of claim 1, wherein the drug is lovastatin and the dosage form provides a mean $AUC_{0\text{-}48hr}$ of lovastatin acid from about 9.96 to about 132.54 ng·hr/ml.

Claim 19. (Original) The controlled release dosage form of claim 1, wherein the drug is lovastatin and the dosage form provides a mean $AUC_{0\text{-}48hr}$ of lovastatin acid from about 47.5 to about 91.2 ng·hr/ml.

Claim 20. (Cancelled)

Claim 21. (Previously presented) The controlled release dosage form of claim 1, which provides a mean maximum plasma concentration (C_{max}) of total HMG-CoA Reductase Inhibitors from about 4.7 ng/ml to about 25.4 ng/ml, based on a 40 mg dose of lovastatin.

Claim 22. (Previously presented) The controlled release dosage form of claim 1, which provides a mean maximum plasma concentration (C_{max}) of total HMG-CoA Reductase Inhibitors from about 10.5 ng/ml to about 17.3 ng/ml, based on a 40 mg dose of lovastatin.

Claims 23-24. (Cancelled)

Claim 25. (Previously presented) The controlled release dosage form of claim 1, which provides a mean maximum plasma concentration (C_{max}) of active HMG-CoA Reductase Inhibitors from about 2.1 ng/ml to about 22.5 ng/ml, based on a 40 mg dose of lovastatin.

Claim 26. (Previously presented) The controlled release dosage form of claim 1, which provides a mean maximum plasma concentration (C_{max}) of active HMG-CoA Reductase Inhibitors from about 6.4 ng/ml to about 13.4 ng/ml.

Claim 27. (Original) The controlled release oral solid dosage form of claim 1, which provides a mean time to maximum plasma concentration (T_{max}) which occurs at about 11 to about 32 hours after oral administration of a single dose of said drug to human patients in the morning.

Claim 28. (Original) The controlled release oral solid dosage form of claim 27, wherein the dosage form provides a mean time to maximum plasma concentration (T_{max}) which occurs at about 16 to about 32 hours after oral administration of a single dose after breakfast (in the fed state).

Claim 29. (Original) The controlled release oral solid dosage form of claim 28, wherein the drug is lovastatin and the dosage form provides a mean maximum plasma concentration (C_{max}) of the drug from about 1.5 ng/ml to about 4.5 ng/ml, based on a 40 mg dose of lovastatin, after oral administration of a single dose after breakfast (in the fed state).

Claim 30. (Cancelled)

Claim 31. (Original) The controlled release oral solid dosage form of claim 1, which when administered in the morning in the fed state, provides a mean time to maximum plasma concentration (T_{max}) which occurs at from about 22 to about 26 hours after administration.

Claim 32. (Original) The controlled release dosage form of claim 1, wherein the drug is lovastatin, said dosage form providing a mean maximum plasma concentration (C_{max}) of lovastatin from about 1.5 ng/ml to about 7.1 ng/ml, based on a 40 mg dose of lovastatin, after administration to human patients.

Claim 33. (Original) The controlled release oral solid dosage form of claim 1, which provides a mean time to maximum plasma concentration (T_{max}) at about 10.4 to about 20.6 hours after oral administration to human patients after administration of a single dose of said drug at dinner time.

Claim 34. (Original) The controlled release oral solid dosage form of claim 33, wherein the drug is lovastatin and the dosage form provides a mean maximum plasma concentration (C_{max}) of said drug from about 1.9 ng/ml to about 4.4 ng/ml, based on a 40 mg dose of lovastatin.

Claim 35. (Original) The controlled release oral solid dosage form of claim 33, which provides a mean time to maximum plasma concentration (T_{max}) at about 13.5 to about 17.5 hours after oral administration at dinner time.

Claim 36. (Original) The controlled release oral solid dosage form of claim 35, wherein the drug is lovastatin and the dosage form provides a mean maximum plasma concentration (C_{max}) of lovastatin of about 3 ng/ml, based on a 40 mg dose of lovastatin.

Claim 37. (Previously presented) The controlled release oral solid dosage form of claim 1, which dosage form provides a mean time to maximum plasma concentration (T_{max}) which occurs at 10 to about 23.2 hours after oral administration to a human patient after administration of a single dose of said drug to human patients at bedtime.

Claim 38. (Original) The controlled release oral solid dosage form of claim 37, which dosage form provides a mean time to maximum plasma concentration (T_{max}) at about 14.2 to about 16.9 hours after oral administration of a single dose of said drug to human patients at bedtime.

Claim 39. (Previously presented) The controlled release oral solid dosage form of claim 1, which dosage form provides a mean time to maximum plasma concentration (T_{max}) at 10 to about 22 hours at steady-state after oral administration to human patients at bedtime.

Claim 40. (Original) The controlled release oral solid dosage form of claim 39, which dosage form provides a mean time to maximum plasma concentration (T_{max}) at about 12 to about 16 hours at steady-state after oral administration to human patients at bedtime.

Claim 41. (Original) The controlled release oral solid dosage form of claim 39, wherein the drug is lovastatin and the dosage form provides a mean maximum plasma concentration (C_{max}) of said drug from about 1 ng/ml to about 8 ng/ml, based on a 40 mg dose of lovastatin.

Claim 42. (Original) The controlled release oral solid dosage form of claim 40, wherein the drug is lovastatin and the dosage form provides a mean maximum plasma concentration (C_{max}) of the drug of about 4 ng/ml, based on a 40 mg dose of lovastatin, after oral administration of a single dose at bedtime.

Claim 43. (Original) The controlled release oral solid dosage form of claim 1, wherein the drug is selected from the group consisting of lovastatin, a derivative of lovastatin, an active metabolite of lovastatin, and mixtures thereof.

Claim 44. (Original) The controlled release oral solid dosage form of claim 3, which provides a mean time to maximum plasma concentration about 14 to about 24 hours after oral administration.

Claim 45. (Original) The controlled release dosage form of claim 44, wherein the drug is lovastatin, said dosage form providing a mean maximum plasma concentration (C_{max}) of lovastatin from about 1.5 ng/ml to about 7.1 ng/ml, based on a 40 mg dose of lovastatin, after administration to human patients.

Claim 46. (Original) The controlled release dosage form of claim 44, wherein the drug is lovastatin, said dosage form providing a maximum plasma concentration (C_{max}) of the drug of from about 3 ng/ml to about 4 ng/ml (based on a 40 mg dose of lovastatin), after administration to human patients.

Claim 47. (Previously presented) The controlled release oral solid dosage form of claim 44, which achieves an accumulation of lovastatin at steady-state conditions of about 1.4- to about 2-fold the levels attained by immediate release lovastatin administered once daily.

Claim 48. (Previously presented) A method for reducing serum cholesterol levels in humans, comprising orally administering a drug comprising an alkyl ester of hydroxy substituted naphthalenes in a controlled release oral solid dosage form which provides a mean time to maximum plasma concentration (T_{max}) of the drug which occurs at 10 to about 32 hours after oral administration of said dosage form to human patients.

Claim 49. (Original) The method of claim 48, wherein the drug is lovastatin and the dosage form provides a mean maximum plasma concentration (C_{max}) of lovastatin from about 1 ng/ml to about 8 ng/ml, based on a 40 mg dose of lovastatin, after administration to human patients.

Claim 50. (Original) The method of claim 48, wherein the drug is lovastatin and the dosage form provides a mean maximum plasma concentration (C_{max}) of lovastatin from about 1.5 ng/ml to about 7.1 ng/ml, based on a 40 mg dose of lovastatin, after administration to human patients

Claim 51. (Original) A method for reducing serum cholesterol levels in humans, comprising orally administering a drug comprising an alkyl ester of hydroxy substituted naphthalenes in a controlled release oral solid dosage form to human patients in the morning, which dosage form provides a mean time to maximum plasma concentration (T_{max}) which occurs at about 11 to about 32 hours after oral administration to human patients.

Claim 52. (Original) The method of claim 51, wherein the drug is lovastatin.

Claim 53. (Original) The method of claim 51, wherein the T_{max} occurs at about 16.3 to about 24 hours after administration.

Claim 54. (Original) The method of claim 51, wherein the drug is lovastatin and the dosage form provides a mean maximum plasma concentration (C_{max}) of said drug from about 1.5 ng/ml to about 6.9 ng/ml, based on a 40 mg dose of lovastatin.

Claims 55-56. (Cancelled)

Claim 57. (Original) The method of claim 51, further comprising administering the dosage form in the morning in the fed state, such that the time to maximum plasma concentration (T_{max}) occurs from about 22 to about 26 hours after administration.

Claim 58. (Previously presented) A method for reducing serum cholesterol levels in humans, comprising orally administering a drug comprising an alkyl ester of hydroxy substituted naphthalenes in a controlled release oral solid dosage form to human patients at dinner time, which dosage form provides a mean time to maximum plasma concentration (T_{max}) at 10.4 to about 20.6 hours after oral administration of a single dose of lovastatin to a population of human patients.

Claim 59. (Original) The method of claim 58, wherein the drug is lovastatin and the dosage form provides a mean maximum plasma concentration (C_{max}) of said drug from about 1.9 ng/ml to about 4.4 ng/ml, based on a 40 mg dose of lovastatin.

Claim 60. (Original) The method of claim 58, wherein the mean time to maximum plasma concentration (T_{max}) occurs at from about 13.5 hours to about 17.5 hours after oral administration.

Claim 61. (Original) The method of claim 60, wherein the drug is lovastatin, and the dosage form provides a mean maximum plasma concentration (C_{max}) of said drug of about 3 ng/ml, based on a 40 mg dose of lovastatin.

Claim 62. (Previously presented) A method for reducing serum cholesterol levels in humans, comprising orally administering a drug comprising an alkyl ester of hydroxy substituted naphthalenes in a controlled release oral solid dosage form to human patients at bedtime, which dosage form provides a mean time to maximum plasma concentration (T_{max}) which occurs at 10 to about 23.2 hours after oral administration.

Claim 63. (Original) The method of claim 62, wherein the drug is lovastatin and the dosage form provides a mean maximum plasma concentration (C_{max}) of said drug from about 1 ng/ml to about 8 ng/ml, based on a 40 mg dose of lovastatin.

Claim 64. (Original) The method of claim 62, wherein the dosage form provides a mean time to maximum plasma concentration (T_{max}) which occurs at about 14.2 to about 16.9 hours after oral administration of a single dose.

Claim 65. (Original) The method of claim 62, wherein the drug is lovastatin and the dosage form provides a mean maximum plasma concentration (C_{max}) of the drug of about 4 ng/ml, based on a 40 mg dose of lovastatin, after oral administration of a single dose.

Claim 66. (Original) The method of claim 62, wherein said T_{max} occurs at about 10 to about 22 hours after oral administration to human patients at steady-state.

Claim 67. (Original) The method of claim 62, wherein said T_{max} occurs at about 12 to about 16 hours after oral administration.

Claim 68. (Original) The method of claim 66, wherein the drug is lovastatin and the dosage form provides a mean maximum plasma concentration (C_{max}) of said drug from about 3 ng/ml to about 8 ng/ml, based on a 40 mg dose of lovastatin at steady-state.

Claim 69. (Original) The method of claim 66, wherein the drug is lovastatin and the dosage form provides a mean maximum plasma concentration (C_{max}) of said drug of about 5.5 ng/ml.

Claim 70. (Previously presented) A method for improving the dose-response relationship achieved via the administration of a statin drug orally administered in immediate release form, comprising orally administering the statin in a controlled release dosage form which provides a mean time to maximum plasma concentration (T_{max}) of the statin drug which occurs at 10 to about 32 hours after oral administration to human patients.

Claim 71. (Previously presented) A method for providing increased systemic bioavailability of lovastatin, while at the same time not increasing the bioavailability of lovastatin acid, compared to an immediate release reference standard form of lovastatin, comprising preparing a controlled release oral solid dosage form of lovastatin which comprises a therapeutically effective amount of lovastatin and a sufficient amount of a controlled release carrier such that the controlled release dosage form provides a dissolution of from about 0% to about 25% lovastatin released after 2 hours; from about 40% to about 85% lovastatin released after 6 hours; and not less than about 75%

lovastatin released after 16 hours, when measured in vitro in a Type 2 USP 23 dissolution apparatus in 2% sodium lauryl sulfate, pH buffer to 7.0 at 37°C and 50rpm, and such that said dosage form provides a mean time to maximum plasma concentration (T_{max}) of said lovastatin from 10 to about 32 hours after oral administration to human patients, and administering said dosage form to human patients on a once-a-day basis.

Claims 72-75. (Cancelled)

Claim 76. (Previously presented) A controlled release oral solid dosage form for the reduction of serum cholesterol levels in humans comprising a therapeutically effective amount of lovastatin and a controlled release carrier in an amount effective to provide a controlled release of the lovastatin when the dosage form is orally administered, the dosage form providing a mean time to maximum plasma concentration (T_{max}) of the lovastatin which occurs at 9.8 to about 18.8 (14.3 ± 4.5) hours after oral administration to human patients at bedtime.

Claim 77. (Previously presented) A controlled release oral solid dosage form for the reduction of serum cholesterol levels in humans comprising a therapeutically effective amount of lovastatin and a controlled release carrier in an amount effective to provide a controlled release of the lovastatin when the dosage form is orally administered, the dosage form providing a mean time to maximum plasma concentration (T_{max}) of the lovastatin which occurs at 10.6 to about 23.2 (16.9 ± 6.3) hours after oral administration to human patients at bedtime.

Claim 78. (Previously presented) A method for reducing serum cholesterol levels in humans, comprising orally administering a therapeutically effective amount of lovastatin in a controlled release oral solid dosage form to human patients at bedtime, which dosage form provides a mean time to maximum plasma concentration (T_{max}) of the lovastatin which occurs at 9.8 to about 18.8 (14.3 ± 4.5) hours after oral administration to human patients at bedtime.

Claim 79. (Previously presented) A method for reducing serum cholesterol levels in humans, comprising orally administering a therapeutically effective amount of lovastatin in a controlled release oral solid dosage form to human patients at bedtime, which dosage form provides a mean time to maximum plasma concentration (T_{max}) of the lovastatin which occurs at 10.6 to about 23.2 (16.9 ± 6.3) hours after oral administration to human patients at bedtime.

Claim 80. (Previously presented) A controlled release oral solid dosage form for the reduction of serum cholesterol levels in humans comprising a therapeutically effective amount of lovastatin and a controlled release carrier in an amount effective to provide a controlled release of the lovastatin when the dosage form is orally administered, the dosage form providing a mean time to maximum plasma concentration (T_{max}) of the lovastatin which occurs at 10.4 to about 20.6 (15.5 ± 5.1) hours after oral administration to human patients with the evening meal.

Claim 81. (Previously presented) A method for reducing serum cholesterol levels in humans, comprising orally administering a therapeutically effective amount of lovastatin in a controlled release oral solid dosage form to human patients at bedtime, which dosage form provides a mean time to maximum plasma concentration (T_{max}) of the lovastatin which occurs at 10.4 to about 20.6 (15.5 ± 5.1) hours after oral administration to human patients with the evening meal.

IX. EVIDENCE APPENDIX

- U.S. Patent No. 5,376,383 to Alberts et al., cited by Examiner in Final Office Action of July 21, 2005
- U.S. Patent No. 5,837,379 to Chen et al., cited by Examiner in Final Office Action of July 21, 2005
- U.S. Patent No. 6,485,748 to Chen et al., cited by Examiner in Final Office Action of July 21, 2005
- Gregory A. McClelland, et al., Enhancement of 3-Hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) Reductase Inhibitor Efficacy Through Administration of a Controlled-Porosity Osmotic Pump Dosage Form, Pharmaceutical Research, Vol. 8., No. 7. 1991, submitted by Appellants in Supplemental Response of of May 23, 2006
- The Physician's Desk Reference, 2006 Edition, pages 2730-2735, submitted by Appellants in Supplemental Response of May 23, 2006

X. RELATED PROCEEDINGS APPENDIX

-None-